ABSTRACT

Coarctation of the aorta is a congenital narrowing or complete obstruction of the thoracic aorta. Associated with this condition is a generalized hypertension. Two conflicting theories have been advanced as to the pathogenesis of the hypertension. The first theory is that the hypertension is mechanical in origin, the high blood pressure being due to the resistance to blood flow produced by the aortic stenosis. The second theory is that the hypertension is of renal origin, the increased blood pressure being produced by some alteration in renal hemodynamics.

We have attempted to demonstrate that the hypertension is of renal origin. Coarctation of the aorta was produced in a series of dogs and following the procedure the animals became hypertensive.

One of the dog's kidneys was then transplanted to the neck and then the remaining kidney was removed so that all functioning renal tissue was proximal to the site of coarctation. Following this procedure there was a prompt return of the blood pressure to normal or sub-normal values in all ten of the complete experiments.

We believe that we have thus indicated that the kidney plays a role in the hypertension associated with Coarctation of the Aorta.

THE UNIVERSITY OF ALBERTA

THE RENAL FACTOR IN THE HYPERTENSION OF EXPERIMENTAL COARCTATION OF THE AORTA

A DISSERTATION

SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

FACULTY OF ARTS AND SCIENCE

DEPARTMENT OF PHYSIOLOGY

by

J. D. M. ALTON

EDMONTON, ALBERTA

JUNE, 1954

ACKNOWLEDGEMENTS

This investigation was carried out with the assistance of grants from the National Research Council under the direction of Dr. R. C. Harrison, to whom the writer wishes to acknowledge his indebtedness.

He would like to express his appreciation for the kind co-operation and assistance of Dr. H. V. Rice of the Department of Physiology and to Mr. B. Fairall for technical assistance.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Coarctation of the aorta is a congenital condition, characterized by stenosis or complete occlusion of the aorta, generalized hypertension, and a marked reduction in life expectancy due to its complications. Two conflicting theories have been advanced to explain the hypertension in this condition. The most obvious, which was widely accepted until the past decade, was that it was mechanical in origin, the hypertension being due to resistance to blood flow through the aortic stenosis.

The second theory is that the stenosis reduces renal arterial flow, with the resultant release of renal pressor substances. Our results in this experiment lend support to this theory.

The kidney was first implicated as a possible cause of hypertension in 1827, when Richard Bright (1) associated evidence of renal damage with cardiac hypertrophy. In the absence of valvular disease of the heart he presumed correctly that the cardiac hypertrophy was due to hypertension. Tigerstedt and Bergmann (2) in 1898 demonstrated that the kidney produced a pressor substance which they called renin. When in 1939 Goldblatt (3) showed that renal artery compression in dogs produced hypertension, the possibility of a renal mechanism in coarctation of the aorta was seriously considered.

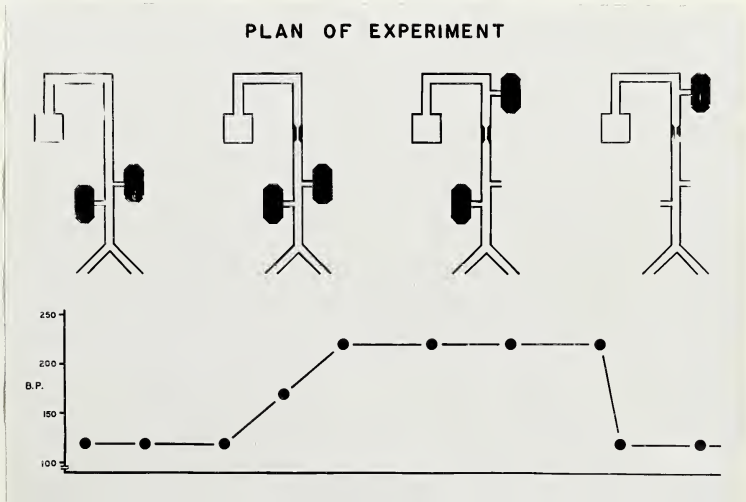
Until Steele (4) used intra-arterial methods to measure pressures in clinical cases of coarctation, it was thought that

hypertension was limited to the areas proximal to the coarctation, with hypotension distally. He showed that there was a diastolic hypertension in the distal vascular bed, with a marked reduction in pulse pressure in this area.

Many attempts have been made to resolve the problem of the mechanical versus the renal mechanism in this disease. These have centered around studies of peripheral resistances, and determinations of renal flow and function. The results of these studies have been conflicting. This will be discussed later in some detail.

We have attempted to answer the question by transplanting the kidney to a site proximal to the ccarctation. Coarctation has been produced in a series of dogs, which has resulted in a very significant degree of hypertension. Following establishment of the hypertension, one kidney has been transplanted to the carotid vessels in the neck. This procedure did not affect the hypertension until the kidney remaining below the coarctation was removed, when a prompt and sustained return to normotension resulted.

The plan of the experiment is illustrated diagrammatically. (Fig. 1.)



HISTORICAL AND CLINICAL ASPECTS OF COARCTATION OF THE AORTA

Coarctation of the aorta has, no doubt, occurred since the beginning of man. However, this malformation of the aorta was apparently not appreciated until about the middle of the eighteenth century.

Mendelson (5) and others considered Morgagni as the first to draw attention to the unusual condition. Abbot (6), Flexner (7) and others have credited Paris, the French anatomist, as being the first to fully describe in 1789 and 1791 the typical pathological features of coarctation of the aorta.

The number of case reports has increased yearly since 1791. By 1928, Abbot (6) was able to report on a series of 200 cases in which post mortem was performed, and in which the "adult" type of coarctation was present. By 1946 a further 104 cases had been collected and reviewed by Reifenstein, Levine and Gross (8).

The common classification of coarctation of the aorta is that of Bonnet (9), who in 1903 distinguished between infantile and adult types. The infantile type is that in which the area of constriction of the aorta is a rather extended one, lying between the origin of the left subclavian artery and the aortic insertion of the ductus anteriosus. This type is rare, usually resulting in death before the age of two years. A patent ductus arteriosus is also present.

The so-called adult type is that in which the constriction is sharply localized, either at the point of insertion of the ductus arteriosus or very close to it. The adult type may be

seen at any age, but is usually recognized in late childhood or early adult life. The ductus in this type is closed.

The gross pathological picture of the interior of the aorta in the adult type of coarctation takes the form of a diaphragm-like structure, lying across the lumen, with a small aperture persisting in most cases. The diameter of the aperture rarely measures more than one millimeter. Distal to the stricture of the aorta there is usually some "post-stenotic" dilatation.

The diagnosis of coarctation of the aorta is not difficult and its recognition depends on carrying out the few simple procedures necessary to exclude coarctation in every case of hypertension.

The important features in the diagnosis of coarctation, according to Christensen and Hines (10), are:

1. Characteristic differences in the arterial pulsations and indirect blood pressures in the upper and lower extremities. The abdominal, femoral, popliteal and tibial arterial pulsations are usually feeble or absent. Most patients have hypertension in the upper extremities and hypotension in the lower limbs by ordinary cuff measurements.

2. The presence of one or more cardiac or cardiovascular murmurs, the most common being a fairly loud, rough, precordial, systolic bruit of maximal intensity over the base of the heart.

3. The presence of a well-developed collateral arterial system that by-passes the coarctation. This occurs particularly in the scapular and interscapular regions as evidenced by the presence of thrills and bruits in these areas.

4. Characteristic erosions seen as "rib-notching" on X-rays. Notching of the ribs may not be conspicuous, as only one or two ribs may be affected, but when seen, Pugh (11) states that it is almost pathognomonic of coarctation of the aorta.

Frequently the patient who has coarctation has no symptoms. The two most common symptoms related to the abnormality are dyspnea and headache. However, Hines and Christensen (12) state that palpitation of the heart, epistaxis, thoracic pain, visual disturbances and intermittent claudication may occur. According to Gross (13), it is four or five times commoner in males than in females.

The prognosis for patients with untreated coarctation of the aorta is poor. According to Reifenstein, Levine and Gross (8), who reviewed autopsy material from 104 cases, about one quarter (26 per cent) of the patients lived a long life, and had little or no incapacitation. About one quarter (22 per cent) died from bacterial endocarditis or aortitis, the infecting organism being the Streptococus viridans. About one quarter (23 per cent) of patients died from sudden rupture of the aorta. About one quarter (28 per cent) died because of the hypertensive state. Deaths from

cardiac failure are about twice as common as fatalities from intra-cranial haemorrhage. The average age of death was 35 years. These statistics indicate that while some persons may live a long and useful life with coarctation of the aorta, the abnormality is one which brings tremendous hazards to its posessor.

The development of surgical techniques for the treatment of coarctation of the aorta began at the turn of the century. Carrel (14)(15) in 1910 and later years made observations on the length of time during which the aorta might be safely occluded, on the dangers of infection, on the various techniques for repair of blood vessels and on transplantation of segments of human popliteal artery as well as homologous grafts of veins into the thoracic aorta of dogs. Blakemore, Lord and Stefko (16) in 1942 successfully bridged defects in the abdominal aorta of animals through the use of their non-suture method, employing a vein graft and vitalluim tubes. In 1944 Blalock and Park (17) devised an operation on experimental animals for circumventing the coarctation by anastomosis of the left subclavian artery to the side of the aorta distal to the point of stenosis. In 1945, Gross and Hufnagel (18) and Crafoord and Nylin (19) reported their experiments on the resection and primary end-to-end anastomosis of the thoracic aorta of dogs.

The first operation on a patient by Crafoord was on October 19, 1944, and that by Gross on June 28, 1945. Clagett (20) was the first to use the subclavian artery to by-pass the point of stenosis in patients. This operation is rarely used at the

present time as often the diameter of the subclavian artery is not equal to that of the aorta.

During the past five years aortic grafts have been used in the surgical treatment of selected cases of coarctation of the aorta. Grafts are particularly suitable if the stenotic area is of any appreciable length and also in those cases of coarctation with the formation of an aneurysm distal to the point of constriction.

In 1952 Glenn and O'Sullivan (21) reported that over 300 cases of coarctation had undergone operation with a constantly decreasing morbidity and mortality rate.

PRODUCTION OF EXPERIMENTAL COARCTATION

The production of coarctation of the aorta in laboratory animals has long been a problem, although it has been successfully done by several methods in recent years.

There are three conceivible methods of attempting to reduce the diameter of the aorta, namely:

(1) External compression

(2) Intramural

(3) Intravascular

External compression of the aorta was used by the earliest investigators in their attempts to treat abdominal and peripheral aneurysms. These were uniformly unsuccessful because of necrosis at the site of compression and invariable secondary haemorrhage.

Halstead (22) reported in 1911 initial success with silver and aluminum bands in bringing about a gradual occlusion of the abdominal aorta in dogs. However, in 1913 he concluded that "ultimately the metal bands must cut through the aorta". Subsequently he used fascia lata and homologous aortic strips (23) to wrap about the aorta, but found, as did Pearse (24), that the strips of fascia either stretched so much they proved ineffective, or they cut through the vessel wall.

In 1939, Page (25) found that ordinary cellophane wrapped about a kidney led to the development of a heavy fibrous capsule which later constricted and produced hypertension in dogs, rabbits, and cats. Shortly thereafter, Pearse (26) produced a complete occlusion of the aorta by banding it loosely with similar material.

In 1942, Owings (27) was successful in eventually ligating the aorta in six out of seventy-five dogs, using rubber bands applied at multiple operations.

The utilization of an intravascular obstruction to accomplish gradual occlusion of the aorta was reported by Reid (28) in 1924. In a small series of six dogs he was able to produce total occlusion of the aorta by introducing intraluminally, rolls of fascia to plug the aorta. Pearse (29) threaded small springs of steel, silver and copper wire into the aorta which brought about varying degrees of stenosis due to thrombosis in the area of the spring. However, this was followed by recanalization. Pearse's (26) attempts to produce a local thrombosis by exposing a segment of the intima of the aorta to fifty per cent glucose and sodium morrhuate were also unsuccessful.

Efforts to reduce the diameter of the aortic lumen by intramural or intrinsic contracture of the vessel wall date back to 1913 when Matas (30) attempted to produce a gradual stenosis of the aortic lumen by multiple plications of the wall in its long axis. These experiments were unsuccessful as relaxation occurred with a gradual tendancy toward the re-establishment of the lumen. Pearse (26), in 1940, attempted to constrict the vessel wall by injecting sodium morrhuate into the media, painting tincture of iodine or twenty-five per cent acriflavine on the wall, and applying a diathermy current with the hope of producing an intrinsic contracture of the vessel wall. None of these attempts resulted in a permanent constriction.

It can be seen from the above mentioned experimental studies that to reduce the diameter of a large artery is a difficult experimental problem, however, in recent years several successful methods have been reported. In 1944, Blalock and Park (17), in devising an operation for coarctation of the aorta reduced the flow through the thoracic aorta by complete ligation of the vessel and then anastomosing the left subclavian to the distal aorta. This procedure did not result in any remarkable change in the blood pressure in upper and lower extremities. However, in 1951, Scott and Bahnson (31) in the same laboratory, used this method to produce experimental coarctation and found that it produced a significant elevation of the blood pressure in the upper extremities. Varco et al (32) succeeded in reducing the aortic lumen by excising a notch or wedge from the aorta of young growing dogs and suturing the defect. Hufnagel (33) showed that segments of the thoracic aorta could be replaced with Lucite plastic tubes with survival of the animal for long intervals. Sealy and McSwain (34), in 1949, using Hufnagel's principle, designed and found practical, a Lucite tube with a stream-lined hourglass constriction which they tied into the aorta. This is the method which we have chosen in our experiments because:

1. It was an easy and reliable method of producing partial aortic occlusion or coarctation.

2. It produces a consistent significant hypertension in the experimental animal. Varco (32) has shown that reduction in size of the thoracic aorta will not result in hyper-

tension unless the aortic diameter is reduced at least 50 per cent, or the cross-sectional area at least 75 per cent. If, on the other hand the occlusion is too great, paraplegia will result in a high percentage of animals. Sealy (35) states that by using the lucite tube method the aorta was reduced in diameter from 75 to 85 per cent.

3. It is a method that can be used in the average dog population. It does not require the use of puppies or young growing animals.

METHODS

The usual precautions against laboratory diseases in the dog population were taken. Moreover, the animals were kept for some weeks prior to operation, with weekly determinations of blood pressure. This allowed those that were going to die of intercurrent infections to do so, and ensured that true pre-operative pressures had become established. We found that pressures tended to be high until the dogs adjusted themselves to laboratory life.

All our dogs were tested for Leptospira infection which is responsible for a rather high incidence of renal disease among the casual dog population. This was carred out in the laboratory of Professor R. D. Stuart (36), Professor of Bacteriology.

Sealy and McSwain's lucite tube, previously referred to, when used in a dog of moderate size, will almost invariably result in hypertension with a very low incidence of paraplegia. This tube is designed to fit into the ends of the divided aorta, and has three outside grooves on either end, so that the aorta can be tied securely over it. It should be mentioned that if too small a dog is used, it is difficult to insert the tube into the divided aorta, and if one is successful, the incidence of hypertension will be low. If the dog is very large, paraplegia will probably result.

B. U. N. determinations were done by the urease method, and were determined by frequent intervals. Renal clearance, renal

flow and estimations of peripheral resistance were not done in this series.

The animals were anaesthetized with intravenous pentothal, which was used for anaesthesia prior to determinations of blood pressures and for the operative procedures. Depth of anaesthesia made a slight difference in pressure determinations and we were careful to maintain a relatively constant depth of anaesthesia. When intrathoracic procedures were being carried out, we maintained pulmonary ventilation by means of the "Pneophore" which converts continuous positive pressure to intermittent positive pressure.

Direct arterial pressures were measured by means of the Sanborn electromanometer and recorded by a modified Sanborn Viso-Cardiette. The Viso-Cardiette was modified by Dr. H. V. Rice so that pressure tracings could be taken at two speeds. The slow speed tracings gave an accurate determination of the systolic and diastolic pressures and the fast speed tracings gave a true picture of the pulse curve. The femoral and carotid arterial pressures were chosen as representative pressures distal and proximal to the coarctation. The femoral artery can be readily punctured, but for ease of repeated carotid artery punctures, it was necessary to transplant the right carotid artery to a subcutaneous position in the neck. This vessel was not divided, but merely mobilized, and the strap muscles and fascia of the neck sutured behind it. The vagus was left in its normal position.

"Pneophore" - Manufactured by Mine Safety Appliances.

A 21-gauge needle was used throughout for arterial punctures. Interposed between the puncturing needle and the recording apparatus, a "Heparin Drive" system was placed. This was designed and constructed by Dr. H. V. Rice on a modification of Hebb's instrument for continuous Penicillin therapy (37). The function of the "Heparin Drive" system was to provide for a minute, continuous flow of heparin through the puncturing needle. A dilute solution of heparin was supplied at a rate of 10 drops per minute, which kept the needle patent at all times, yet did not interfere with pressure recordings. Carotid and femoral systolic, diastolic and mean pressures were taken at frequent intervals, with several determinations, days or weeks apart, between each stage of the experiment. Mean pressures were recorded on the electromanometer by the electrical integrator.

In general, three pressures were taken at weekly or bi-weekly intervals before any operative procedures were done. Those dogs whose systolic pressure remained above 150 mm. of mercury were discarded as unsuitable for this experiment. For this reason about one-quarter of our available dogs had to be rejected. Following coarctation , pressures were taken twice weekly for three to four weeks, and then monthly until they were stabilized at hypertensive levels. Following transplant of one kidney to the neck vessels, pressures were recorded weekly or every second week until they were stable, and then the second kidney was removed. Pressures were done immediately following nephrectomy on either the first, second, third, or

fourth post-operative day (but only once during this period in each dog), and were then done weekly for a month. Following this, they were done monthly.

Aseptic surgical technique was used throughout. Penicillin and sulphadiazine were used post-operatively in the early cases, but later discontinued as they were found to be unnecessary.

Following is a typical protocol:

1953	Dog #43	Weight 15 Kilo.
June 1	Admitted to laboratory.	Isolated for 2 weeks.
June 14	Given 9 c.c. pentothal	I.V. Femoral pressure 150/120 mm.
June 21	Given 9 c.c. pentothal	I.V. Femoral pressure 160/120 mm.

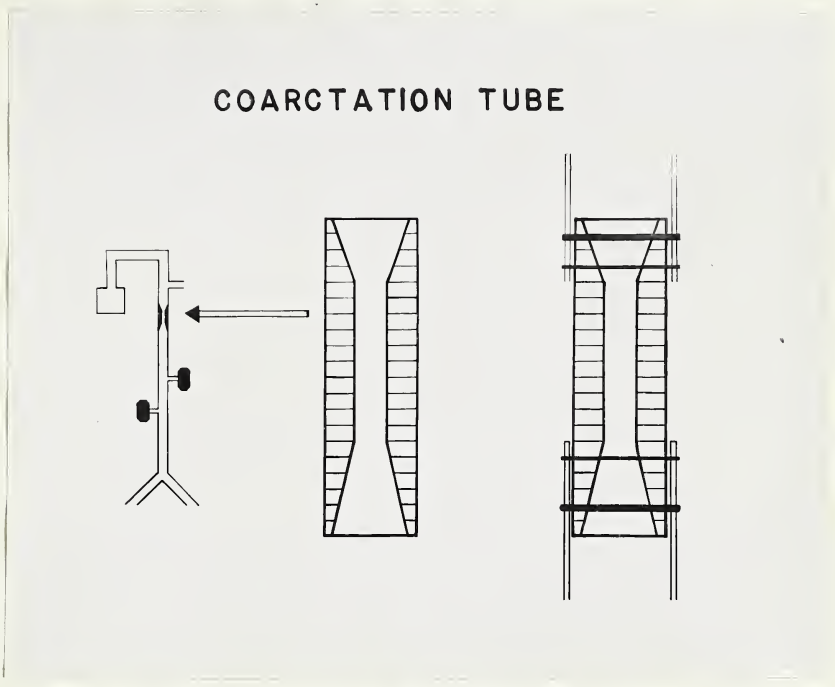
June 28 Given 9 c.c. pentothal. Carotid transplant done. Carotid pressure - 150/130 mm. of mercury. Femoral pressure - 150/120 mm. of mercury. The left chest was clipped, the skin painted with tr. iodine, and an intravenous of 5% G.D.W. was started. More pentothal was introduced into the I. V. tubing as necessary during the course of the operation. An endotracheal tube with attached cuff was inserted into the trachea and the cuff inflated. The laboratory air line was attached to the endotracheal tube with the pneophore interposed to maintain artificial respiration. The air pressure and pneophore were adjusted to provide adequate depth and frequency of respirations.

The chest was opened through the left fifth interspace, the inferior pulmonary ligament divided, and the lung retracted.

The parietal pleura was divided over the descending aorta from the first to the seventh intercostal arteries, and the four pair of intercostal arteries from two to five inclusive, were divided between ligatures. About three inches of aorta was mobilized.

Potts clamps were then placed on the mobile aorta about two inches apart, and the aorta divided between them. (We first used Blalock clamps, but found Potts less traumatic to the intima and more secure.) Two sutures of 000 silk were passed through the cut ends of the aorta, and at either side (3:00 and 9:00 o'clock), left untied. These were very useful in stabilizing the aortic segments and facilitated introduction of the lucite tube. The lucite tube was then inserted into the cut ends of the aorta, and the previously mentioned sutures tied. This held the tube in position until the ligatures were placed and secured. Because of retraction, the aortic segments only surrounded the proximal and distal quarters of the tube, each end of which had three circumferential grooves cut in the outside surface. A pair of ligatures was placed at either end to firmly secure the aorta to the tube. Obviously, a very tight ligature would result in necrosis of the aortic wall beneath and distal to it. Such a tight ligature was, however, necessary to prevent the aortic segment from slipping off the lucite tube. This pair of ligatures was placed, one at either end, to engage the aorta near the cut ends, and tied tightly into the innermost grooves. The second pair was of #3

silk, and tied loosely to hold the aortic wall in contact with the tube. (See Fig. 2.)



The Potts clamps were loosened slowly (distal one first), and the parietal pleura carefully re-approximated over the operative site. (It was hoped that this combination of ligatures would prevent secondary haemorrhage, and this proved to be so only if these ligatures were correctly placed and tied.) The aortic occlusion time was seven minutes.

The chest was closed and aspirated of residual air. The dog received 300 c.c. of 5% G.D.W. No special diet or medication was used.

Post coarctation pressures were:

1953.

July 5 Carotid 190/150 mm. of mercury. Femoral 160/140 mm. of mercury.

July 15 Carotid 200/150 mm. of mercury. Femoral 170/150 mm. of mercury.

July 23 Carotid 210/160 mm. of mercury. Femoral 150/130 mm. of mercury.

Aug. 19 Carotid 210/160 mm. of mercury. Femoral 160/140 mm. of mercury.

Sept. 21 Carotid 210/170 mm. of mercury. Femoral 160/150 mm. of mercury.

Oct. 23 Carotid 210/160 mm. of mercury. Femoral 170/150 mm. of mercury.

Dec. 10 Carotid 210/160 mm. of mercury. Femoral 170/140 mm. of mercury.

Subsequent to the pressure determinations, the left loin and neck of the dog were clipped, the skin painted, and the areas draped. Through a vertical incision in the neck, overlying the strap muscles, and extending from hyoid to sternum, the external jugular vein and common carotid artery were freed in their entirety. The skin and platysma muscle posterior to the incision were freed from their underlying tissues to prepare a subcutaneous bed for the left kidney. The adventitia was freed from the common carotid just proximal to its bifurcation, and from the external jugular vein at the same level.

The left kidney was then removed from its retroperitoneal position through a muscle splitting incision, parallel to, and just below the costal margin. The renal vessels were dissected free to the aorta and vena cava and divided individually, renal artery first. The full length of both vessels was obtained partly because this was often necessary to reach the main vessel beyond its bifurcation, and also because full length was needed.

in the neck. The ureter was divided as far inferiorly as possible. The renal fascia was left in the abdomen and the adrenals were not seen, handled, or interfered with. The distal end of the ureter, spermatic or ovarian vein and the stumps of the renal vessels were ligated with 00 silk. No clamps or ligatures were placed on the vessels to be used in the anastomosis.

Without waiting to close the retroperitoneal wound the kidney was placed in the subcutaneous tissues of the neck, and the ends of the renal vessels cleared of their adventitia.

Bulldog clips were placed inferiorly on the neck vessels, tied superiorly, and the vessels divided. Using 000000 arterial silk, an end to end everting intima to intima anastomosis, tied at three points (Carrel), was effected between the common carotid and renal arteries. During the anastomosis, a few drops of 10% heparin were frequently applied to the region of the anastomosis. Following the completion of the arterial suture, the bulldog clip on the carotid was removed for a few pulsations and the kidney flushed with arterial blood. The renal vein and external jugular vein were then similarily sutured, care being taken here to ensure that the vessels were not rotated on their long axis. Each procedure took 15 minutes, (10 to 20 minutes). All clamps were then removed, and urine began to flow from the ureter in two minutes (1/2 to 60 min.)

The kidney capsule was then tacked to the deep tissues of the neck with three or four interrupted sutures of 0000 silk. The ureter was placed in its most direct position leading to

the skin of the neck. The skin at this point was picked up under tension with a skin needle, and a disc of full thickness skin about 3 mm. in diameter was excised. This left a skin defect of almost double this diameter. The subcutaneous tissues deep to this were spread freely, and the ureter brought out as a cutaneous ureterostomy. The excess was excised and mucosa to skin sutures of dermalon placed in each of the four quadrants. When these were tied, the ureteral stoma was held widely open by skin tension. Four additional interrupted sutures were placed. The neck wound was drained and closed, as was the abdominal wound.

During this procedure, which lasted two and one half hours, the dog received 500 c.c. of G.D.W. intravenously. No particular post operative care was given, the dog being returned to the kennels the following day.

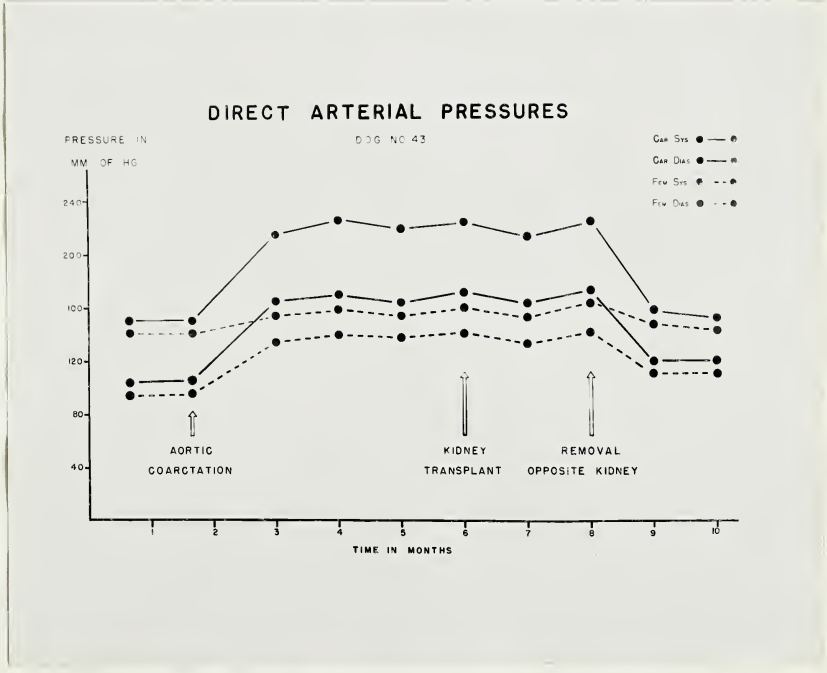
Pressures were repeated on the 16th day of December. The Carotid artery pressure was 210/170 mm. of mercury, and the Femoral artery pressure 180/150 mm. of mercury.

Pressures on January 8th, 1954 were: Carotid 210/180, and Femoral 170/140. Following determinations of pressures, the right kidney was removed, using a procedure similar to that for kidney transplant, except that no attempt was made to obtain any length of renal vessels. This procedure of contralateral nephrectomy only required one-half hour. The kidney was sectioned, placed in fixative, and sent for pathological examination.

1954 Pressures subsequently were:

Jan.	11	Carotid 130/110 mm. of mercury.	Femoral 130/110 mm. of mercury.
Jan.	18	Carotid 160/140 mm. of mercury.	Femoral 160/140 mm. of mercury.
Feb.	8	Carotid 150/135 mm. of mercury.	Femoral 120/100 mm. of mercury.
March	15	Carotid 155/120 mm. of mercury.	Femoral 130/115 mm. of mercury.
April	12	Carotid 160/130 mm. of mercury.	Femoral 120/100 mm. of mercury.

Figure 3 is a diagrammatic representation of the blood pressure changes during the various stages of the experiment in Dog Number 43.



RESULTS

As can be seen from Table I, forty-one dogs had thoracotomies, in an attempt to produce Coarctation, performed. Seventeen died during or soon after thoractomy, and all of these except one (distemper) were due to technical errors. These all occurred early in our series and were due to careless handling of the intercostal vessels, inexperience with anaesthesia, and ignorance of the tension required in the ligatures about the aorta. The thrombosis in the tube was secondary to rupture of the aortic intima by the Blalock clamps.

All those that survived the first month following thoracotomy became hypertensive. Three died following development of hypertension, as noted. Eight dogs (controls) have not had any further surgery, and have remained hypertensive. In some of the dogs the hypertension has slowly progressed. (See Table II.)

Thirteen had a kidney transplanted to the neck. Three died, as noted. The remaining ten subsequently had a contralateral nephrectomy. Five of this ten are still alive and well, with no significant increase in B.U.N. The longest survival of this group has had a "neck kidney" for eleven months, and has had this kidney as its solitary kidney for nine months. Although he has been blind for a year, he is well nourished and active. His pressures have been normal for nine months, (following contralateral nephrectomy) but his hypertensive ocular damage was apparently irreversible.

TABLE I SUMMARY OF OPERATIVE RESULTS

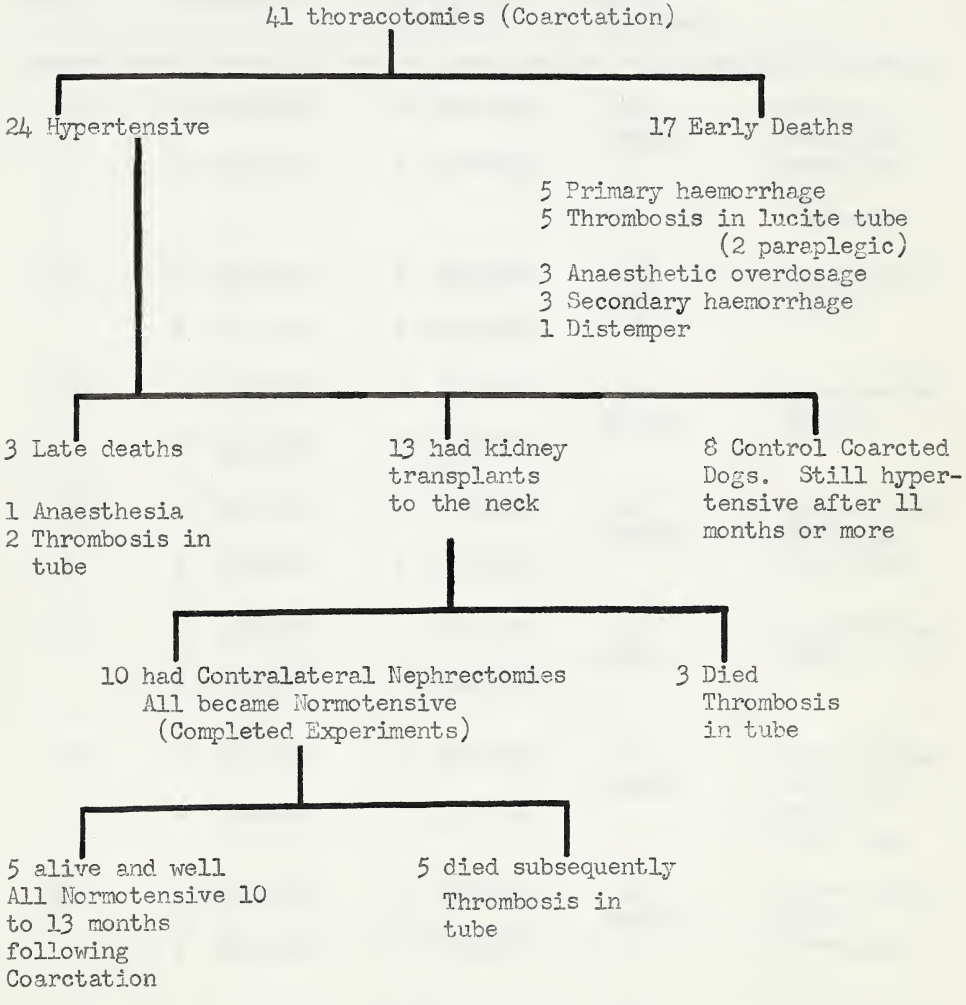


TABLE II SUMMARY OF CONTROL COARCTED DOGS

Dog No.	Original Pressures	Pressures at Time of Writing	Length of Time Coarcted	Comments
5	C 140/110	C 210/180	12 months	Hind leg Paralysis Sacrificed P.M. - Aneurysm
	F 150/110	F 150/140		
15	C 140/100	C 220/180	16 months	Hypertension Stable
	F 140/100	F 170/150		
17	C 140/120	C 260/220	16 months	Hypertension Stable
	F 140/110	F 160/150		
18	C 150/120	C 290/210	15 months	Hypertension Gradually Increasing
	F 150/100	F 180/170		
20	C 140/110	C 220/190	14 months	Hypertension Stable
	F 140/100	F 190/170		
30	C 140/120	C 190/180	13 months	Hypertension (moderate) Stable - small dog
	F 140/110	F 150/140		
40	C 140/100	C 220/190	12 months	Hypertension Still Increasing
	F 140/110	F 190/180		
41	C 135/115	C 280/220	11 months	Hypertension Still Increasing
	F 135/105	F 180/170		

The five who died subsequently to contralateral nephrectomy apparently died as a result of thrombosis in the region of the tube. It is thought that the sudden drop in blood pressure following nephrectomy aided this development.

The degree of occlusion of the thoracic aorta produced by the lucite tube was determined in a series of 15 dogs used in the experiments. In each instance the distended aorta, denuded of parietal pleura, was measured metrically, in situ during surgery, with Vernier calipers. A reduction was made for total aortic wall thickness of 3 mm. as computed from examination of a series of dogs at post mortem. The cross sectional area in this series of dogs was reduced an average of 85 per cent, the range being from 81 to 93 per cent.

In 34 of the animals who had coarctation tubes placed in their aortas, the aortic occlusion times were measured. See Table III. In the first half of the series the average occlusion time was 10.8 minutes, whereas in the second half of the series, the time averaged 7.4 minutes. The overall average aortic occlusion time for the 34 dogs was 9 minutes. Sealy and McSwain (34) report a high incidence of spastic paraplegia if the aortic occlusion time exeeds 25 minutes.

TABLE III AORTIC OCCLUSION TIMES

Dog No.	Time	Dog No.	Time
5	9 min.	27	9 min.
6	17 min.	28	7 min.
7	12 min.	29	9 min.
10	9 min.	30	10 min.
11	9 min.	31	8 min.
14	12 min.	32	6 min.
15	8 min.	33	8 min.
17	7 min.	34	7 min.
18	8 min.	35	6 min.
19	10 min.	36	12 min.
20	11 min.	37	11 min.
21	11 min.	38	6 min.
22	11 min.	39	7 min.
23	17 min.	40	5 min.
24	11 min.	41	6 min.
25	11 min.	43	7 min.
26	10 min.	44	6 min.
First Half	Average = 10.8 min.	Second Half	Average = 7.4 min.

Overall Average = 9 min.

Table IV shows the pressure determinations in the ten dogs that have been completed. In this series of ten dogs 180 pressure determinations were made, averaging 18 per dog over the course of the experiment. The carotid systolic (C.S.) and diastolic (C.D.), femoral systolic (F.S.) and diastolic (F.D.) pressures have been averaged during the periods:

Prior to Coarctation (Normal Dogs) - Column (3)

Following Coarctation (Co.) only - Column (4) and (6)

Following Coarctation and Kidney Transplant (K.T.) - Column (7)

Following Coarctation, Kidney Transplant, and Contralateral Nephrectomy (C.N.) - Column (8) and (10)

At the bottom of the table the C.S., C.D., F.S., and F.D. pressures are compared in the whole series.

By determining the B.U.N. on a series of apparently normal dogs, we found a normal range of 10 - 20 mgms. %. The highest B.U.N. determination in our series was 43 mgms. %. We are satisfied that none of the dogs are uremic, and that none have died of uremia. The present B.U.N. levels in the five dogs that have only a "neck kidney" are 22, 43, 25, and 34 mgms. %. The longest survival, previously referred to, has the lowest B.U.N.

Microscopic examination of the kidneys removed from the hypertensive dogs at the time of contralateral nephrectomy has been negative, although special studies of the juxtaglomerular area are not yet complete.

TABLE IV

TABLE

(1) Dog No.	(2) Site of Pressure Determination	(3) Average Pressure Before Coarctation	(4) Average Pressure Following Coarctation Only	(5) Change in Pressure
		mm. of Hg.	mm. of Hg.	mm. of Hg.
11	C.S.	140	208	+68
	C.D.	120	189	+69
	F.S.	140	178	+38
	F.D.	120	173	+53
24	C.S.	140	191	+51
	C.D.	120	161	+41
	F.S.	150	142	+8
	F.D.	105	138	+33
25	C.S.	140	194	+54
	C.D.	120	161	+41
	F.S.	145	127	−18
	F.D.	110	121	+11
28	C.S.	150	194	+44
	C.D.	130	170	+40
	F.S.	150	122	+28
	F.D.	115	120	+5
32	C.S.	135	199	+64
	C.D.	120	169	+49
	F.S.	133	166	+33
	F.D.	108	159	+51
33	C.S.	170	211	+41
	C.D.	150	169	+19
	F.S.	175	175	±0
	F.D.	135	148	+11
35	C.S.	150	203	+53
	C.D.	120	157	+37
	F.S.	150	170	+20
	F.D.	110	153	+43
36	C.S.	150	206	+56
	C.D.	120	177	+57
	F.S.	150	200	+50
	F.D.	110	156	+46
43	C.S.	150	208	+58
	C.D.	130	160	+30
	F.S.	155	162	+7
	F.D.	120	144	+22
44	C.S.	170	210	+40
	C.D.	130	165	+35
	F.S.	160	172	+12
	F.D.	125	152	+27

Summary

Percentage Change in Pressure Resulting from Coarctation of Aorta Only

Carotid Systolic +34.6% Femoral Systolic +12.2%

Carotid Diastolic +33.8% Femoral Diastolic +26.6%

(6) Change in Pressure	(7) Average Pressure Following Co. and K. T.	(8) Average Pressure Following Co. and K.T. and C. N.	(9) Change in Pressure From Before Coarctation (Col.(3))	(10) Change in Pressure From Before Coarctation (Col.(3))
%	mm. of Hg.	mm. of Hg.	mm. of Hg.	%
+48.5	188	149	+ 9	+6.0
+ 57.5	150	123	+ 3	+ 2.0
+ 27.1	160	127	-13	- 9.0
+ 44.1	150	118	- 2	- 2.0
+36.4	200	130	-10	- 7.1
+34.1	160	110	-10	- 8.3
+ 5.3	155	120	-30	-20.0
+31.4	145	110	+ 5	+ 4.7
+38.6	200	126	-14	-10.0
+34.1	180	106	-14	-11.6
-12.4	150	63	-82	-56.5
+10.0	150	63	-47	-42.7
+29.3	215	130	-20	-13.3
+30.7	190	110	-20	-15.3
+18.6	140	100	-50	-33.3
+ 4.3	140	90	-25	-21.7
+47.4	200	137	+ 2	+ 1.4
+40.8	140	113	- 7	- 5.8
+24.8	180	97	-36	-27.0
+47.2	150	93	-15	-13.8
+24.1	211	157	-13	- 7.6
+12.6	150	123	-27	-18.0
± 0	170	108	-67	-32.8
+ 8.1	130	98	-37	-27.5
+35.5	200	170	+ 20	+ 13.3
+30.8	150	130	+10	+ 8.3
+13.3	175	170	+ 20	+13.3
+39.0	155	140	+30	+27.2
+37.3	205	155	+ 5	+ 3.3
+47.5	180	140	+20	+16.6
+33.3	205	172	+22	+14.6
+41.8	160	142	+32	+29.1
+25.8	210	150	0	0.0
+23.1	175	127	-3	- 2.3
+ 4.5	175	130	-25	-16.1
+18.3	145	113	- 7	- 5.8
+23.5	200	155	-15	- 8.8
+26.9	165	125	- 5	- 3.8
+ 7.5	165	150	-10	- 6.2
+21.5	140	130	+ 5	+4.0

of Table

Percentage Change in Pressure Resulting from Coarctation Plus K.T. and C.N.

Carotid Systolic -2.28% Femoral Systolic -17.84%

Carotid Diastolic -3.36% Femoral Diastolic -4.85%

Autopsies conducted on those hypertensive dogs which have died, show an early development of atheromatous degeneration in the great vessels proximal to the coarctation. We anticipate that this will be more marked in those animals that have survived a year or more.

DISCUSSION

Although this experiment was planned five years ago, and begun in 1951, it is not original, in that it was reported from Dr. Blalock's laboratory soon after we began (31). Their method of production of coarctation was less reliable, and their series smaller. This is a confirmation of their findings, with additional data in a larger series.

We have demonstrated that the kidney is involved in the production of hypertension in experimental coarctation of the aorta. We have invariably found that the dogs remain hypertensive until all renal tissue has been transplanted from the area distal to the stenosis to a point proximal to the stenosis. Pressures then return to normotensive levels, although the aortic coarctation remains. Actually, as can be seen from the Summary of Table IV, the systolic pressure in the great vessels distal to the coarctation (F.S.) is considerably reduced (18%). This is expected, because of the still existing coarctation. The mechanical effect of the aortic narrowing reduces the amplitude of the pulse wave.

The production of coarctation with hypertension in this series of dogs appears to simulate the clinical condition.

Although this experiment demonstrates that the kidney is involved in the production of hypertension, it does not necessarily follow that it is entirely responsible. It is fair to state that the kidney appears to initiate the chain of events that leads to the production of hypertension in coarctation of the

aorta. Once established, it is not necessarily irreversible, for transplant of the kidney to a site where its circulation is normally maintained apparently stops the secretion of pressor substances. Whether this will occur if the hypertension has been of long duration remains to be investigated.

Coarctation of the aorta appears to affect renal circulation in the same manner as a Goldblatt clamp. The manner in which renal circulation is affected is as yet, an unsolved problem.

Compare the vascular dynamics of the kidney above the coarctation with that of the kidney below the coarctation (Table IV, Col. (7)). They are both in a hypertensive environment. All pressures in both zones are increased. The least increase is the systolic pressure distal to the coarctation (F.S.), but even it is elevated. Why is the abdominal kidney secreting pressor substances?

Page (38) (39) and his associates, used a kidney perfusion technique, delivering oxygenated blood through the renal artery under varying systolic, diastolic and pulse pressures. They demonstrated increased liberation of renin from the kidneys in the renal venous blood by addition of renin-activator and perfusion of the mixture through isolated organs. They concluded that the reduction of pulse pressure is the stimulus eliciting the out-pouring of renin. In our experiments (Table V) the average pulse pressure in the distal zone was reduced to less than half by the coarctation. However, in one large animal, it was not reduced (#36), and in another (#33), only reduced by one third. This theory, then, is not entirely adequate.

TABLE V SUMMARY OF PULSE PRESSURE DETERMINATIONS OF TEN "COMPLETED" DOGS

Dog Number	Average Femoral Pulse Pressure Before Coarctation	Average Femoral Pulse Pressure Following Coarctation
11	20	8
29	45	7
25	35	9
28	35	6
32	25	11
33	40	26
35	40	17
36	40	43
43	35	18
44	45	20
Average in 10 dogs	36	16

There is, of course, a difference in the dynamics of the two areas, although we cannot define it. In human cases of long duration the atheromatous degeneration in the great vessels proximal to the coarctation is much more marked than in the distal zone. As pointed out by Willis (40), hypertension is only one of the etiological factors in the production of atherosclerosis.

In our experiment the reduction in pressures is not due to operative shock, or blood loss. Of the three operative procedures, namely, coarctation, kidney transplant, and nephrectomy, only the last is followed by a reduction in pressure. It is by far the least traumatizing procedure.

Although a mechanical explanation for the hypertension of coarctation seems reasonable at first glance, further thought should make one skeptical. It is unreasonable to presume that the body could not compensate for this obstruction by the development of collaterals. On biological grounds it is most unlikely that such an obstruction would result in more than a temporary hypertension in the proximal zone. All of the experimental work supporting the mechanical theory has been done as acute experiments, the duration of the aortic obstruction being a matter of minutes or hours. We duplicated these experiments during the production of coarctation by recording the carotid and femoral pressures during the operative procedure. When the Potts clamps were applied to the aorta, the femoral pressure dropped to nearly zero. After the lucite tube was tied into the aorta, and the clamps removed, pressures returned to normal in a few minutes, except for a reduction

in the femoral systolic, (dampening of the pulse wave). Yet the aorta was sufficiently obstructed by the tube that a slowly developing hypertension, which reached 200 mm. of Hg. (carotid systolic), developed in three weeks time. Had the hypertension developed on a mechanical basis in this series of dogs, it would have been maximal immediately following the coarctation procedure, and then fallen as collaterals developed.

Resection of the coarctation in young clinical cases is more quickly and frequently followed by a return to normal pressures than in the adult cases, where pressures often remain hypertensive. Yet, in all these the obstructing lesion has been removed. In no instance do they return promptly to normal. It has been said that in the older cases the failure is due to arteriosclerosis. It is more likely that the mechanism is no longer primarily renal. In our dogs it took many days (20 to 60) for the hypertension to develop, yet pressures return to normal within four days following contralateral nephrectomy. This occurred in spite of the fact that the aorta was still mechanically obstructed by the lucite tube. We are unable to explain the slow onset and rapid disappearance of the hypertension in our series.

The proponents of the mechanical theory invariably quote the case (41) of a girl with coarctation of the aorta below the renal vessels, and associated hypertension. Apparently, this is the only case of this type in the literature. She undoubtedly had hypertension and coarctation below the renal

arteries. The occlusion was immediately below the renal arteries, and judging from the picture of the specimen the aorta begins to narrow proximal to the origins of the renal vessels. There were multiple atheromatous plaques in the aorta proximal to the stenosis, and it was thought that these might have given rise to emboli. The appearance of the kidneys grossly and microscopically is not noted. Two possibilities come to mind in this case. The renal vessels may have been partially obstructed by the hypoplastic aorta. Her hypertension might have been due to nephritis or some cause unrelated to the coarctation. Scott and Bahnson (31) transplanted two kidneys to the groin in their series, and then removed the other kidney. Pressures remained hypertensive.

There are many unanswered questions in this clinical condition, and in this experiment. What change in haemodynamics stimulates the kidney to produce pressor substances? Studies of renal blood flow and filtration rates in humans have been conflicting.

Genest (42) found a diminution in renal blood flow preoperatively, as did Friedman (43), who also found a normal filtration rate. He attributed the normal filtration rate to an efferent arteriolar constriction. Post operatively, most of the patients showed an increase in renal blood flow.

Harris, (44) while confirming the pre-operative findings, stated that the increased renal blood flow post-operatively was only temporary, and returned to pre-operative levels in

two to four months. None of the investigators were able to establish a parallel relationship between systemic blood pressures and renal blood flow.

They did fail to demonstrate any evidence of marked impairment of renal artery flow. If there is a renal mechanism in the hypertension of coarctation of the aorta it is not due to renal "ischaemia". The changes that occur in renal flow are far more subtle than this. A repetition of these studies in experimental animals might be illuminating.

Studies of peripheral resistance have also been carried out in clinical cases of coarctation of the aorta. An increase in peripheral resistance has been demonstrated in essential hypertension and in experimental renal hypertension.

Poiseuille's Law (45) states in part, that resistance is proportional to the pressure and inversely proportional to the flow. In the upper extremities normal blood flow has been found by Pickering (46), Lewis (47) and Wakim (48); decreased flow by Printzmetal and Wilson (49), and increased flow by Bing (50). This diversity of results is probably due to the difficulty in accurately determining peripheral blood flow. It remains that there is no reliable evidence of any change in blood flow in the upper extremities. If it is normal, peripheral resistance is certainly increased, as the pressures are hypertensive.

Blood flow in the areas distal to the aortic coarctation has also been investigated. Lewis (47) found them normal, as did Wakim (48), using the venous occlusion plethysmograph.

Lewis points out that intermittent claudication is rarely a complaint of these patients, and believes that this is evidence in favor of normal leg flow. Bing (50), however, found leg flow decreased, and Hull (51) believes that many of these patients have clinical evidence of decreased blood flow, such as cold feet, numbness, and skin pallor.

It is fair to state that studies of peripheral resistance in patients have been inconclusive. The weight of evidence points, however, to a generalized increase in peripheral resistance in human coarctation of the aorta. This is in favour of a non-mechanical explanation for the hypertension.

Other approaches to the problem might include determinations of the Renin content of the systemic blood, or of the renal vein, or the use of cross circulation techniques to establish the presence of pressor substances in the hypertensive dogs.

The effect of adrenalectomy should be studied.

SUMMARY

1. Experimental coarctation of the aorta with hypertension has been produced in a series of dogs which resembles clinical coarctation.

2. Although the precise mechanism leading to the production of the hypertension is still to be determined, it is initiated by a renal mechanism.

3. A mechanical explanation for the hypertension in this condition is inadequate.

BIBLIOGRAPHY

(1) BRIGHT, Richard: Reports of Medical Cases Selected with a view of Illustrating the Symptoms and Cure of Diseases by a Reference to Morbid Anatomy.
London, Longman and Co., 1827.

(2) TIGERSTEDT, R. and BERGMANN, P. E.: Skand. Arch. Physiol. 8 : 223, 1898.

(3) GOLDBLATT, H., KAHN, J. R., and HANZAL, R. F.: Studies on Experimental Hypertension. The Effect on Blood Pressure of Constriction of the Abdominal Aorta Above and Below the Site of Origin of Both Main Renal Arteries.
J. Exper. Med. 69 : 649, 1939.

(4) STEELE, J. M.: Evidence for General Distribution of Peripheral Resistance in Coarctation of the Aorta.
J. Clin. Investigation. 20 : 473, 1941.

(5) MENDELSON, C. L.: Pregnancy and Coarctation of Aorta.
Am. J. Obst. and Gynec. 39 : 1014, 1940.

(6) ABBOT, Maude E.: Coarctation of the Aorta of the Adult Type, II. A Statistical Study and Historical Retrospect of 220 Recorded Cases with Autopsy of Stenosis or Obliteration of the Descending Arch in Subjects Above the Age of Two Years.
Am. Heart J. 3 : 392, 1928.

(7) FLEXNER, James: Coarctation of the Aorta (Adult Type). Clinical and Experimental Studies.
Am. Heart J. 11 : 572, 1936.

(8) REIFENSTEIN, G. H., LEVINE, S. A., and GROSS, R. E.: Coarctation of the Aorta. A Review of 104 Autopsied Cases of the "Adult Type", 2 Years or Older. Am. Heart J. 33 : 146, 1947.

(9) BONNET, L. M.: Sur la lesion dite stenose congenitale de l'aorte dans la region de l'isthme. Rev. de Med. 23 : 108, 1903.

(10) CHRISTENSEN, N. A. and HINES, E. A.: Clinical Features in Coarctation of the Aorta: A Review of 96 Cases. Proc. Staff Meet., Mayo Clinic. 23 : 339, 1948.

(11) PUGH, D. G.: The Value of Roentgenologic Diagnosis in Coarctation of the Aorta. Proc. Staff Meet., Mayo Clinic. 23 : 343, 1948.

(12) HINES, E. A. and CHRISTENSEN, N. A.: Diagnosis and Prognosis in Cases of Coarctation of the Aorta. Proc. Staff Meet., Mayo Clinic. 22 : 121, 1947.

(13) GROSS, R. E.: Surgical Treatment for Coarctation of the Aorta. Experiences from 60 Cases. J. A. M. A. 139 : 285, 1949.

(14) CARREL, Alexis: On the Experimental Surgery of the Thoracic Aorta and the Heart. Ann. Surg. 52 : 83, 1910.

(15) CARREL, Alexis: Ultimate Results of Aortic Transplantation. J. Exper. Med. 15 : 389, 1912.

(16) BLAKEMORE, A. H., LORD, J. W., and STEFKO, P. L.: The Severed Primary Artery in the War Wounded; a Non-suture Method of Bridging Arterial Defects. Surgery. 12 : 488, 1942.

(17) BLALOCK, A. and PARK, E. A.: Surgical Treatment of Experimental Coarctation of the Aorta.
Ann. Surg. 119 : 445, 1944.

(18) GROSS, R. E. and HUFNAGEL, C. A.: Coarctation of the Aorta; Experimental Studies Regarding Its Surgical Correction.
New England J. Med. 233 : 287, 1945.

(19) CRAFOORD, C. and NYLIN, G.: Congenital Coarctation of the Aorta and Its Surgical Treatment.
J. Thoracic Surg. 14 : 347, 1945.

(20) CLAGETT, O. T.: Coarctation of the Aorta: Surgical Aspects.
Proc. Staff Meet., Mayo Clinic, 22 : 131, 1947.

(21) GLENN, F. and O'SULLIVAN, W. D.: Coarctation of the Aorta.
Ann. Surg. 136 : 770, 1952.

(22) HALSTEAD, W. S.: Partial Progressive and Complete Occlusion of the Aorta and Other Large Arteries in the Dog by Means of the Metal Band.
J. Exper. Med. 11 : 373, 1911.

(23) HALSTEAD, W. S.: Partial Occlusion of the Thoracic Aorta and Abdominal Aorta by Bands of Fresh Aorta and Fascia Lata.
Tr. Am. Surg. Ass. 31 : 218, 1913.

(24) PEARSE, H. E.: The Impracticability of Using Fascia for the Gradual Occlusion of Large Arteries.
Am. J. Surg. 16 : 242, 1932.

(25) PAGE, I. H.: The Production of Persistent Arterial Hypertension by Cellophane Perinephritis.
J. A. M. A. 113 : 2046, 1939.

(26) PEARSE, H. E.: Experimental Studies on the Gradual Occlusion of Large Arteries.
Ann. Surg. 112 : 923, 1940.

(27) OWINGS, J. C. and HEWITT, F. F.: Successful Experimental Ligation and Division of the Thoracic Aorta.
Ann. Surg. 115 : 596, 1942.

(28) REID, M. R. : Partial Occlusion of the Aorta with Silk Sutures and Complete Occlusion with Fascial Plugs.
J. Exper. Med. 40 : 293, 1924.

(29) PEARSE, H. E.: A Method for the Gradual Occlusion of the Aorta.
S. G. O. 46 : 411, 1928.

(30) MATAS, R. and ALLEN, C. W.: Conclusions Drawn from an Experimental Investigation Into the Practicability of Reducing the Caliber of the Thoracic Aorta by a Method of Plication or Infolding of its Walls by Means of a Lateral Parietal Suture Applied in One or More Stages.
Ann. Surg. 58 : 304, 1913.

(31) SCOTT, H. W. and BAHNSON, H. T.: Evidence for a Renal Factor in the Hypertension of Experimental Coarctation of the Aorta.
Surgery. 30 : 206, 1951.

(32) CLATWORTHY, H. W., SAKO, Y., CHISHOLM, T. C., CULMER, C., and VARCO, R. L.: Aortic Coarctation.
Surgery. 28 : 245, 1950.

(33) HUFNAGEL, C. A.: Permanent Intubation of the Thoracic Aorta.
Arch. Surg. 54 : 382, 1947.

(34) SEALY, W. C. and McSWAIN, C. H.: A Method for Producing Coarctation of the Thoracic Aorta in Dogs.
Surgery. 25 : 451, 1949.

(35) SEALY, W. C., DeMARIA, W., and HARRIS, J.: Studies of the Development and Nature of the Hypertension in Experimental Coarctation of the Aorta.
S. G. O. 90 : 193, 1950.

(36) McINTYRE, W. I. M., STUART, R. D.: Canine Leptospirosis,
Vet. Record. 61 : 411.

(37) HEBB, H. D.: An Instrument for Continuous Penicillin Therapy.
C. M. A. J. 54 : 602, 1946.

(38) KOHLSTAEDT, K. G., and PAGE, I. H.: The Liberation of Renin by Perfusion of Kidney Following Reduction of Pulse Pressure.
J. Exper. Med. 72 : 201, 1940.

(39) PAGE, I. H. and CORCORAN, A. C.: Experimental Renal Hypertension. Springfield, Illinois, 1948.
Charles C. Thomas.

(40) WILLIS, G. C.: Localizing Factors in Atherosclerosis,
C. M. A. J. 70 : 1, 1954.

(41) D'A. MAYCOCK, W.: Congenital Stenosis of the Abdominal Aorta.
Am. Heart J., 13 : 633, 1937.

(42) GENEST, S., NEWMAN, E. V., KATTUS, A. A., SINCLAIR-SMITH, and GENECIN, A.: Renal Function Before and After Surgical Resection of Coarctation of the Aorta.
Bulletin of John Hopkins Hospital. 83 : 429, 1948.

(43) FRIEDMAN, M., SELZER, A., and ROSENBLUM, A.: Renal Blood Flow in Coarctation.
J. Clinical Invest. 20 : 107, 1941.

(44) HARRIS, J. S., SEALY , W. C., De MARIA, W.: Hypertension and Renal Dynamics in Aortic Coarctation.
Am. J. Medicine. 9 : 734, 1950.

(45) GLASSER, O.: Medical Physics, Vol. 2 : P. 246. Chicago, The Year Book Publishers, 1950.

(46) PICKERING, G. W.: Peripheral Resistance in Persistant Arterial Hypertension.
Clinical Science. 2 : 209, 1936.

(47) LEWIS, T.: Material Relating to Coarctation of the Aorta of the Adult Type.
Heart. 16 : 205, 1933.

(48) WAKIM, K. G., SLAUGHTER, O., and CLAGETT, O. T.: Studies on the Blood Flow in the Extremities in Cases of Coarctation of the Aorta.
Proc. Staff Meet., Mayo Clinic. 23 : 347, 1948.

(49) PRINZMETAL, M., and WILSON, C.: The Nature of the Peripheral Resistance in Arterial Hypertension with Special Reference to the Vasomotor System.
J. Clin. Investigation. 15 : 63, 1936.

(50) BING, R. J., HANDELSMAN, J. C., CAMPBELL, J. A., GRISWOLD, H. E., and BLALOCK, A.: Surgical Treatment and the Physiopathology of Coarctation of the Aorta.
Ann. Surg. 128 : 803, 1948.

(51) HULL, E.: On the Evidence for Generalized Arteriolar Constriction in Coarctation of the Aorta. Am. Heart J. 35 : 980, 1948.